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13. ABSTRACT (Maximum 200 words) An epidemiologic investigation of a cluster of cases of phyllodes tumors of the female breast was undertaken. A total of 114 cases with biopsy confirmation have been identified. Most were in northern New Jersey. The occurrence of multiple primary phyllodes tumors in a single patient was found to be significantly more frequent than in prior series. Investigations concerning phyllodes tumor occurrence in neighboring counties did not reveal any other regions of increased incidence. Developmental efforts for a phyllodes tumor tissue repository linked to epidemiologic data were begun.			
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FOREWORD

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In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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Starla H. Weiss 9/15/98
PI - Signature Date

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INTRODUCTION

BACKGROUND:

Phyllodes (formerly termed cystosarcoma phyllodes) tumors of the breast are uncommon breast neoplasms, accounting for about 0.5% of primary breast neoplasms¹. These tumors are fibroepithelial tumors composed of an epithelial and a cellular stromal component. This tumor typically occurs in women from 30-69, peaking at age 40-49.

The age-adjusted annual incidence rate of malignant phyllodes tumors is 2.1 per million women. In one of the largest reported case series from the United States, over a period of 78 years (1913 to 1990), 60 patients (59 women, 1 man) who were treated at the Mayo Clinic were confirmed to have phyllodes tumors. This represents an average of only about one case per year. A more recent study in California of malignant phyllodes tumors found that the incidence rates were substantially higher in the 1980's than in the 1970's with the highest rates in *Latino* whites.² They noted that the epidemiology was strikingly different from that of the more common histologic types of breast cancer.² In the largest single case series published, from Poland, none of 170 phyllodes patients had multiple primary tumors.³

The differentiation of benign phyllodes tumors from benign fibroadenomas can be uncertain based on cytopathology alone,⁴ so follow-up biopsy is recommended if a phyllodes tumor is suspected. In our current study, we have tabulated as cases only women who have had biopsy-confirmed diagnoses of a phyllodes tumor; since some women did not have biopsies despite fine-needle aspirates suggestive of a phyllodes tumor, our data will somewhat underestimate the benign cystosarcoma phyllodes tumors.

This study represents a collaboration between the New Jersey Medical School (NJMS) of the University of Medicine and Dentistry of New Jersey (UMDNJ) and Englewood Hospital and Medical Center (EHMC). This project has financial support for some of its activities from agencies other than the U.S. Army. These sources of support are the Englewood Hospital and Medical Center Research Fund, the Foundation of UMDNJ (Principal Investigator (PI) = Dr. Joan Skumick), a National Cancer Institute Cancer Education grant (PI = Dr. Elizabeth Alger) which helps support student summer research and UMDNJ-NJ Medical School research funds.

SCOPE OF WORK and HUMAN USE ISSUES

The scope of work has been modified twice, as approved by the U.S. Army on June 6, 1997 (concerning request dated February 2, 1996) and on August 28, 1997 (concerning request dated August 14, 1997). The grant Performance Period is 15 August 1994 through 30

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September 1998.

As per the approved 2 February 96 modification, the "interviews" were deleted from the original required Scope of Work. The remainder of activities in the grant were in the "exempt" category. We also added a new component, which received Human Use approval prior to implementation related to the development of a Tissue Repository.

In the original scope of work, we proposed that interviews would be conducted using U.S. Army funds, including during the first year. However, our proposed study design involved interviewing cases and controls by telephone with verbal consent, and some funding from other sources (as noted above) had permitted us to begin interviewing prior to the Army grant award. This approach was not consistent with Army Human Use guidelines. However, the study had already been approved by the Institutional Review Boards (IRB) of both the New Jersey Medical School-UMDNJ and EHMC, and is permitted under DHHS and NIH guidelines). Thus, after extensive discussions amongst the Army, the NJMS IRB, and the PI it was agreed to modify the scope of work is so that no Army funds were utilized to conduct these interviews. It should be noted that since only very limited funds were originally allocated in the budget towards this proposed activity, the necessary budget modification was limited. The PI volunteered to add a replacement component to the Scope of Work, as noted above.

Thus, during the first two years of this project, the U.S. Army grant funds were utilized exclusively for activities that meet the criteria for an "exempt" review under DHSS human use guidelines. This work included study design issues, forms design, data base design and programming, systems programming, entry of collected data without personal identifiers, and data analysis. This has remained the prime focus during the final time period as well. Since June 6, 1997 the new component, which received Army Human Use approval, and concerns beginning the development of a Tissue Repository, was begun and has received support from this grant.

PURPOSE OF THE CURRENT WORK

The purposes of this grant are to:

- 1) conduct standard epidemiologic analyses of data to characterize potential risk factors
- 2) summarize findings in appropriate forums
- 3) continue to assess the geographic bounds of phyllodes cases in our region of New Jersey
- 4) solicit written consent to enable the development of a tissue repository.

BODY

OVERVIEW

At Englewood Hospital and Medical Center (EHMC, located in Englewood, Bergen County, New Jersey), Drs. Miguel Sanchez, Rosalyn Stahl and colleagues from 1987 through 1997 have diagnosed a total of 114 women with new cystosarcoma phyllodes tumors. An outside breast pathologist (Paul Peter Rosen, M.D., Sloan Kettering Memorial Cancer Center, New York) formally reviewed the slides in a subset of the initial cases prior to the initiation of this grant and confirmed the diagnosis of cystosarcoma phyllodes. Thus, our current series at EHMC is among the largest to date in the United States, representing diagnoses at a single local medical center over a relatively short period of time. This accumulation of cases provides a unique opportunity to better characterize and understand this rare tumor. We reported our initial epidemiologic findings at the 1997 Army Era of Hope meeting.⁵ The data in this report, of course, supersede the preliminary data included in that extended abstract.⁵

All phyllodes cases were documented by joint review of biopsy histology by Drs. Sanchez and Stahl according to the criteria of Rosen and Rosai⁶. Clinical follow-up data were reviewed to determine rates of phyllodes tumor recurrence and of new tumors in the case series. Pathology and surgical operative reports provided important information to confirm the tumor clinical history in the event further information was required.

GEOGRAPHIC ANALYSES

In 1997, we systematically surveyed hospitals in a five county region to ascertain the phyllodes tumor diagnosis rates in other neighboring institutions and for the counties over an 11.5-year period (1986 through June 1997). In 1995, we had done a similar but less extensive survey of 4 of these same counties. Both times, we worked directly with the chief pathologist (or their designate) at each institution to try to ascertain as accurately as possible the number of benign and malignant phyllodes cases. Based upon the data analyses below, it appears warranted to re-assess the data in conjunction with these pathologists. In particular, revised case counts from some hospitals may lead to further refinement and revision of the county rates.

HOSPITAL SURVEYS, 1997 and 1995

This portion of the project was conducted by surveying all hospitals performing breast biopsies in the region around EHMC, our index hospital. Thirty-eight hospitals in Bergen, Morris, Hudson, Essex, and Passaic Counties were contacted and thirty-seven participated. Located in Bergen County, the one hospital not responding to our study, Hospital "H", had claimed in the past that they diagnosed as many as eight benign and one malignant phyllodes tumor per year yet had no easily retrievable documentation for any case. This hospital did not provide any information beyond that already provided in 1995; it performs an average of 18,000 surgical cases per year.

The Chief of Pathology at each hospital was contacted to obtain the yearly numbers of malignant and benign phyllodes tumors diagnosed between January 1, 1986 and June 30, 1997. (Data from 1986 was not available from EHMC.) These numbers were determined by institutions in several ways. Twenty-four pathologists consulted cross index cards and other colleagues to give us estimates as their department had not yet incorporated a computer retrieval system. (A manual search through all pathology records, page by page, would otherwise be required.) Yet given the rarity of the phyllodes tumor, many pathologists claimed that their number was accurate as they clearly would remember this unusual diagnosis. The remaining fourteen hospitals ran full computer searches to retrieve records of the tumor.

It is very likely that though most hospitals were able to provide us with both the numbers of benign and malignant phyllodes tumors per year, the number of malignant tumors was the more accurately reported figure. In the state of New Jersey, health institutions are required to report malignant lesions to a tumor registry. Thus, many pathologists without access to an automated retrieval system consulted the tumor registry records for cases of the malignant tumor. Indeed, three hospitals were only able to provide information obtained from the tumor registry so their number of benign tumors remains unknown. Another potential limitation in the data concerning the benign phyllodes tumors is that sixteen pathologists reported not differentiating among sub-types of fibroadenomas in their diagnoses reports. Though all sixteen chief pathologists claimed they would not call a benign phyllodes tumor a fibroadenoma, absolute certainty could only come from a time-consuming independent pathology research review of all fibroadenomas. When examining the hospitals' statistics, it is found that out of twenty-five hospitals reporting any cases of phyllodes tumors over the past eleven and a half years, fifteen documented more cases of malignant phyllodes tumors than benign. This is in direct contrast to the majority of published literature as well as our index hospital. For example, Treves and colleagues⁷ studied a series of seventy-seven patients with phyllodes tumors where only eighteen cases were malignant. In addition, EHMC had ninety-nine women with only benign phyllodes tumors and only eleven with malignant phyllodes tumors in the past ten and a half

years. This strengthens our conviction that while the tabulation of malignant phyllodes tumors is probably reasonably accurate, the tabulation of benign phyllodes tumors from certain institutions is likely to be incomplete.

The number of surgical specimens accessioned ("surgicals") by the each department was also obtained for each year. Whenever possible, we also obtained the number of surgicals performed on breast tissue by the institution. Since hospitals widely vary in size and specialty, these numbers are useful denominators to compare hospital-specific rates. Although the number of breast surgicals performed by an institution would be the optimal denominator to use in our calculations, the lack of computer systems made this number impossible to obtain from the majority of hospitals without a tedious manual search. Therefore, since the total number of surgical specimens could be uniformly obtained, this surrogate was used as a standard denominator in our calculations.

Using these numbers, the incidence of benign, malignant, and total phyllodes tumors were calculated in several manners. The rate per 100,000 surgicals was tabulated by hospital for each year and over the eleven and a half years of the study. Rates by county per year and for the period January 1, 1986 to June 30, 1997 were also calculated. County prevalence rates were next calculated, using the 1990 United States census data for the number of women over the age of 16 (retrieved from a government database on the Internet by year and total study period).

Nine hospitals were surveyed in Hudson County, reporting ten phyllodes tumors. Three institutions reported not having diagnosed a phyllodes tumor since 1986, two hospitals reported one case since 1986, and four hospitals reported two cases of phyllodes tumors. The incidence in Hudson County over the 11.5 year period were a total of 2.51 phyllodes tumors per 10^5 surgicals and 3.74 tumors per 10^6 adult women (over the age of sixteen). The malignant rates were 2.01 per 10^5 surgicals and 2.99 per 10^6 adult women.

Six hospitals were contacted in Passaic County, reporting thirteen phyllodes tumors. Amongst these institutions, one hospital reported no cases, four hospitals reported one to two cases, and one hospital reported eight cases (performing about twice as many surgicals as the other hospitals). The incidence rates in Passaic County were a total of 3.61 tumors per 10^5 surgicals and 6.02 per 10^6 adult women. The malignant rates were 1.95 per 10^5 surgicals and 3.24 malignant phyllodes per 10^6 adult women.

Of the four hospitals in Morris County, only one hospital (with two cases) reported diagnosing any phyllodes tumors. The incidence rate's in Morris County were a total of 3.64 phyllodes tumors per 10^5 surgicals and 1.01 per 10^6 adult women. The malignant rates were 1.82 per 10^5 surgicals and 0.50 per 10^6 adult women.

Essex County included thirteen hospitals performing breast procedures that reported eighty-eight cases of phyllodes tumors. Five hospitals reported not having

diagnosed a phyllodes tumor since 1986, six hospitals reported one to five phyllodes tumors, one hospital documented twelve cases, and St. Barnabas Medical Center reported sixty-four cases. Overall, Essex County had 10.15 phyllodes tumors per 10^5 surgicals and 23.31 phyllodes tumors per 10^6 adult women. One hospital has not yet provided its breakdown of malignant and benign tumors.

The overall rates for the above four counties were 6.72 total phyllodes tumors per 10^5 surgicals and 10.65 per 10^6 adult women.

Bergen County, the site of our index hospital, also contains five other health institutions, which qualify for the study. Unlike the four other counties, all hospitals reported cases of phyllodes tumors. Two hospitals reported one to four cases, one hospital reported twelve cases, and Holy Name Hospital reported fourteen cases. As mentioned previously, EHMC has documented one hundred and ten cases and Hospital H has only provided estimates. (Fifteen women had multiple phyllodes tumors at EHMC but were counted by us only once, deflating the EHMC total; it is uncertain whether other hospitals made this adjustment.) The incidence rates for Bergen County were calculated in several manners. Excluding Hospital H, Bergen County still reported a significantly greater 25.95 phyllodes tumors per 10^5 surgicals and 34.33 tumors per 10^6 adult women compared to the four counties above (rate ratios (RR) = 3.86 and 3.22, 95% confidence intervals = 3.04 - 5.01 and 2.54 - 4.18, respectively). Malignant rates were 4.23 per 10^5 surgicals and 5.60 per 10^6 adult women. If the undocumented eight benign and one malignant phyllodes tumors per year estimated by Hospital H are included, the rates rise to 31.78 phyllodes tumors per 10^5 surgicals and 55.27 tumors per 10^6 adult women, intensifying the divergence between Bergen and the other four neighboring counties. The malignant rates including Hospital H estimates were 4.62 per 10^5 surgicals and 8.03 per 10^6 adult women. Finally, excluding our index hospital but including the Hospital H estimate, the Bergen County statistics were 19.42 per 10^5 surgicals and 28.49 per 10^6 adult women. Malignant rates were 3.65 per 10^5 surgicals and 5.36 per 10^6 adult women.

The hypothesis of geographic clustering in the Bergen County area was strengthened by close examination of the Holy Name Hospital data. This institution is located 2.6 miles from EHMC in the neighboring town of Teaneck and is the closest hospital to our index institution. Although Holy Name Hospital only processes an average of 8,455 surgicals a year and is smaller than most of the institutions in the study, it has reported 3 cases of malignant phyllodes tumors and eleven cases of benign phyllodes tumors evenly distributed over the past eleven and a half years. This high incidence in an independent hospital in close proximity to our index hospital, as well as the possible high rate at Hospital H, lends support to the idea that there may be an unexplained excess of phyllodes tumors in a very specific area of New Jersey.

A comparison of EHMC and St. Barnabas Medical Center also suggests apparent geographic clustering. St. Barnabas is located in Livingston, in Essex

County. Like EHMC, St. Barnabas has a large breast care center whose pathologists are well informed concerning phyllodes tumors and have diagnosed sixty-four cases. St. Barnabas has been computerized for the entire time period of the study, and documented information was easily retrievable from this institution. From January 1, 1987 to June 30, 1997, St. Barnabas had 266,329 surgicals while EHMC had 111,822 surgicals. Therefore, St. Barnabas processed 2.4 as many surgicals compared to EHMC. Yet EHMC had 110 cases of phyllodes tumors, almost twice as many as at St. Barnabas. We were also able to obtain the number of breast surgicals performed at each institution over the years 1991 - 1997, a much more accurate denominator to calculate incidence (since the proportion of all breast surgicals was not constant over the period). A women undergoing a breast procedure at EHMC was 7.7 times more likely to have a phyllodes diagnosis (1.79% vs. 0.24%) than at St. Barnabas ($p < 10^{-8}$, $\chi^2 = 136.7$, df = 1). It is notable that the rate at St. Barnabas is comparable to expectations from the literature. St. Barnabas's large series contributes to Essex having the second highest county rates, but Bergen County (excluding Hospital H) still has significantly higher rates (RR = 2.55 and 1.58 for surgicals and adult women, respectively, 95% C.I. 1.99 - 3.41 and 1.22 - 2.12). Thus, the experiences of these similar institutions support a concentration of phyllodes tumors in Bergen County.

In a further updated analysis, we found an overall rate of 9.6 phyllodes tumors (6.2 benign, 3.4 malignant) per million women per year (MWY) in Passaic, Essex, Hudson and Morris counties, comparable to expectations. In contrast, the Bergen County [our index county, where EHMC is located] rate was significantly higher, 34.3 (28.7 benign, 5.6 malignant) per MWY. The rate ratios were 3.6 (95% CI 2.8-4.7) overall, 4.6 (95% CI 3.5-6.4) for benign and 1.7 (95% CI 0.93-2.9) for malignant tumors.

In summary, our data are in favor of geographic localization. Whereas it may be argued that there is increased awareness of the tumor in the area, considerable attention is usually paid to the diagnoses of malignant tumors and it unlikely that these would be missed by institutions in the other counties. Since we had also systematically surveyed nearly all of these same pathologists in 1995 (two years previously), no surge in phyllodes diagnosis had occurred in this intervening period. The suggestion of clustering opens up the question of what potential factors might cause this phenomena and additional approaches to exploring the geographic aspects of our EHMC case series.

ADDITIONAL GEOGRAPHIC ANALSYES

Two sets of new collaborations were developed to explore the geographic aspects. Considerable time and effort was spent clarifying addresses to enable coding using Geographic Information Systems (GIS) software, which requires exact street addresses and

additional research when these do not match to standardized databases.

Dan Wartenberg, Ph.D. at the Robert Wood Johnson Medical School in Piscataway is in the process of statistical assessments of clustering in our study^{8,9}. His preliminary results support geographic clustering of this tumor. Preliminary analysis of the addresses at the time of diagnosis from our case-control data suggests that the cases are more highly clustered geographically than age- and time-matched controls.

Cindy Brewer, Ph.D., a geographer at the University of Pennsylvania, and Charles Frank assisted with the graphing of the residential location. This was done both for our cases, at the time of their phyllodes diagnosis, and the matched control. **Figure 1** in the Appendix shows the cases as a large dot and controls as a small dot. (A color version of this also displayed the age.) Since some cases very closely overlap, some dots overlap partially or almost completely. It is of interest that in the circled southeastern region there are only 6 controls but 13 cases. This section includes both North Bergen (Bergen County) and West New York (Hudson County), which are very near the New Jersey Meadowlands.

Exploration of the U.S. Environmental Protection Agency (EPA) databases provides information on watersheds (**Figures 2, 3** pages) as well as numerous facilities with known contaminants, including Super Fund sites. Color-coded GIS data maps, including data concerning such facilities, are being constructed by the PI and his staff using these EPA databases to assist in further evaluating the regions of interest. Prototypic mapping examples are included in the Appendix as **Figures 3 and 4**. These are presented to demonstrate the potential of the methodology and should not be interpreted as implicating any specific site at this time; literally hundreds of sites exist in these areas of New Jersey. These data may be useful in planning studies that utilize our Tissue Repository (discussed below) to assess whether specific environmental substances may be involved.

In **Figure 5** (prepared for us by Dr. Brewer), only our cases are graphed. There is a visual suggestion of possible clustering of the malignant cases (dark bulls-eye circles), and also of the cases with multiple primary phyllodes tumors (data in red and not displayed on enclosure). Analyses with Dr. Brewer were limited to the exploratory visual presentation of clinical tumor characteristics (benign/malignant, one/multiple primaries), year of occurrence (temporal assessment), and some demographic data (age, race, income). Statistical analyses will involve the collaboration with Dr. Wartenberg.

CASE SERIES AND CASE-CONTROL ANALYSES

In depth information collected by interview from 92 women with phyllodes tumors ("cases") and one age- and time-matched control (without a past history of breast cancer or breast fibroadenoma) for 90 of these interviewed cases, as part of a case-control study were available for analysis. Analyses were also conducted on the clinical and demographic information concerning the entire group of 114 cases.

There was no statistically significant temporal pattern,. The peak occurrence was in 1991.

Year	87	88	89	90	91	92	93	94	95	96	97
Number of cases	7	13	9	14	23	9	12	8	10	2	7

Our cases occurred predominantly among Caucasians (84 women, 74%). There were also 17 (15%) Latina, 7 (6%) Black and 6 (5%) Asian. Cases were significantly more likely to be non-white and non-Jewish compared to the matched controls. Cases were significantly more likely to be Latina than controls (6%).

The 11 women with malignant tumors (mean 40.2 y/o, standard deviation [SD] 14.2, range 21-69) were significantly older than the 103 with benign tumors (mean 33.3 y/o, SD 8.7, range 16-51), p=.02 (ANOVA).

Marital status at the time of phyllodes diagnosis was 36% never married, 56% married, 8% divorced. Cases were somewhat more likely to be never married than controls (22%), p=.07. Cases were significantly more likely to be in the lowest income brackets than controls (46% vs., 31%, p<.05).

Cases tended to develop physically somewhat later than controls, with older ages for menarche and full height. Cases were significantly less likely to have a history of vaginal infection(s) or of sexually transmitted diseases than controls.

Cases had a significantly greater history of reported male relatives with cancer (p=.009, OR=3), and specifically males with lung cancer (p=.06, OR = 2.9). The fathers of seven cases had lung cancer compared to none of the fathers of controls (p=.01). Although many case families presented unremarkable cancer history genograms, in some families there may be an inherited pattern.

Phyllodes tumors can occur within the spectrum of "classic" Li-Fraumeni syndrome.¹⁰ Specific p53 gene mutations have been described in Li-Fraumeni syndrome¹¹ and yet other

p53 mutations in breast cancer¹². Specific p53 mutations in phyllodes tumors have been reported¹³ and the pattern of p53 expression has been examined^{14,15}. It is also intriguing (based on our observation from the case-control study of excess paternal lung cancers) that an expanded Li-Fraumeni-like syndrome may include lung cancers. Laboratory based studies, to further define these issues based upon our case series which is much larger than any so far analyzed, may help to elucidate biologic mechanisms of phyllodes tumors as well as more general mechanisms of carcinogenesis.

Tumor Recurrences

Seven women have had recurrent tumors, including one woman who developed metastatic disease.

Whereas only 4.5% (3/66) tumors with adequate surgical margins recurred, 6.1% (2/33) with "other" margins recurred (relative risk 1.3, p=NS). However, it should be noted that our definitions for primary phyllodes tumors were rigorous. If two instances of ambiguous recurrences had been classified as primary tumors rather than as (presumptive) recurrences, and a possible recurrence that has so far only been documented by FNA was counted as a documented recurrence, the risk rises to 6.0 (p=.11). The recurrence rate in our series, in any event, is significantly lower than in other series (23.1%; see Appendix, Table 1 which is explained in the next section), reflecting the aggressive surgical treatment that had been in practice at EHMC towards controlling this tumor.

Multiple Primary Phyllodes Tumors

Sixteen women (14% of the 114, or nearly 1 in 7) in our series had multiple biopsy-proven phyllodes tumors. Most of these reflected bilateral phyllodes tumors. Five women (4.5%) developed new primary tumors at 0.66, 1.79, 1.79, 2.10 and 2.22 years of follow-up.

The women with multiple primary phyllodes tumors (MPPT) were more likely to be Latina (6/16, 37%) than the women with a single primary (SP) (11/98, 11%), p=.015, and to be younger (p=.023). Several age-dependent factors tended to be less common among the MPPT. The MPPT were more likely to have lower income (83% vs. 41%, p=.01) and reduced body mass index. However, they had similar menstrual and gynecologic histories.

Our occurrence of multiple primaries of 14% was significantly more frequent than in the Polish series³, in which this phenomena apparently did not occur, $p < 10^{-6}$ (binomial distribution).

We undertook an extensive literature review to critically further assess this issue (Appendix, **Table 1**). We identified 32 distinct published studies from 13 countries. (Case series reported more than once in the literature are referenced with both citations but listed only once.) These included cases diagnosed from 1912 through 1996. One of these 32 studies (from Los Angeles County) differed in being from a cancer registry and had no follow-up data, no data on benign phyllodes tumors, and probably could not have identified a woman with multiple phyllodes primaries. Excluding that study leaves 31 distinct series with 1611 reported patients. Of these, 904 were benign (49.9%), 172 borderline (10.7%), 413 malignant (25.6%), and 233 the pathologic status was not stated (many of these were probably benign) or unknown (Table 1).

There were 9 women with bilateral phyllodes tumors at initial presentation, and 2 others were later diagnosed with a contralateral primary phyllodes tumor. Two women had documented multiple unilateral phyllodes.

There were another 5 women who may have had multiple unilateral primaries, 4 at the outset and 1 later on. Although the documentation and criteria to differentiate the possibility of multiple unilateral primary tumors from a single tumor (since phyllodes tumors can be large and spread widely within a breast) or recurrence were lacking or inadequate, for the purposes of statistical comparison the conservative assumption is to assume they might be multiple primaries. Thus, if all of these are assumed to represent instances of multiple primaries, this review of the worldwide published literature gives a grand total of 18 cases (with only 13 are well-documented).

In our series, there are 16 cases, more than the entire number of previously well-documented instances of women with multiple primary phyllodes tumors reported in the literature.

The proportion of women who have multiple phyllodes tumors from our worldwide review of phyllodes case series is 1.12% (18/1611). This is not surprising given the rarity of the tumor. It is important to note that the 14% rate in our EHMC series is significantly higher. This suggests that a candidate definition of an "epidemic" phyllodes case in our series might be any woman in our region with multiple phyllodes primaries. Although this definition would undercount the scope of the problem, it is likely to be useful in analyzing laboratory and epidemiologic data.

DEVELOPMENT OF TISSUE REPOSITORY

We contacted, primarily by mail (but including telephone contact when necessary to update last known addresses), women who had a confirmed diagnosis of a phyllodes tumor to obtain written consent for the future use of their stored specimens for research studies. No new specimens and no clinical procedures were collected as part of this grant. An introductory letter was sent along with the consent form. We had two versions of the letter, depending upon whether or not we had previously interviewed the woman. For the women previously interviewed, we simultaneously also requested return of a form in which they acknowledged in writing their prior voluntary telephone interview, since this placed a minimal added burden on the respondent yet provided a written record of their prior consent. Army grant resources were utilized in soliciting these consents.

As stated in the consent form, for those women from whom written permission was received we now have the ability to be able to retain linkage to all other accrued data in developing and testing a tissue repository. All specimens are being retained at the Pathology Department at Englewood Hospital and Medical Center. The original slides, and in most instances residual tissue blocks as well, have been identified.

If written permission for linked testing is not received, it is necessary to code existing data, including such steps as the exclusion of personal identifiers, prior to utilization for research testing. This would enable us to perform unlinked testing of residual biologic material while retaining some critical information. Prior to sending any such specimen to a laboratory, identified by a unique repository code number, we would irrevocably break linkage by destroying the link between the personal identifier and the new code number. Some specimens would be linked to each other (but not to the woman) in cases where multiple specimens from a single woman exist to enable assessment of sequential data and ensure that a given woman is not multiply counted in statistical analyses. No grant resources have been used for actual laboratory testing, which is outside the scope of the Scope of Work. For some of the cases from EHMC, the women have moved and contact between them and their EHMC physicians has not occurred recently. Thus, it will not be possible to contact some of these women. As efforts to obtain additional written consents remains in progress for others, we have deferred testing of specimens and not yet broken linkage. Furthermore, due to the heterogeneity of phyllodes tumors, some specific laboratory tests under consideration may require special procedures when processing the tissue blocks to ensure the most useful specimen.

Through August 15, 1997, 40 cases had returned consent forms and 38 women (95%) agreed to participate in the linked laboratory study, a very high acceptance rate. Analysis of the return process at that point indicated that personal follow-up by telephone had been

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helpful in leading to the return of forms. We thus anticipated that this approach might lead to significantly more responses, many of which are likely to be agreement for linked study. We confirmed with statistical power calculations that this follow-up process work would be warranted in the development of a tumor registry large enough to initiate laboratory assessments. Indeed, essentially each positive response to the consent forms was an important contribution to statistical power. For example, if the prevalence of a factor X is 50% among cases and laboratory test T carries a 4-fold increase in risk, then if 36 women are studied, $p=0.047$ for a 1-tailed analysis (Fischer's exact test) but $p=0.094$ for a 2-tailed analysis. When the study size is increased by just 33% to 48 women, both 1-tailed ($p=.02$) and 2-tailed analyses ($p=0.04$) would be significant. Thus, the decision was made to spend additional effort towards this task.

As of September 30, 1998, one case had died (from metastatic phyllodes). Of the remaining 113, 10 declined linked research testing (5 verbally and 5 in writing). One person agreed verbally but had not returned all of the consent forms. Of the remaining 102, for 79 we have signed written consents. Of the remaining 23 cases (known or presumed to still be alive), several have indicated willingness to participate so additional efforts are anticipated to obtain additional written consents to enable linked testing and forestall the necessity of breaking linkage for these cases who still may wish to participate.

Since some laboratory studies we plan to analyze will be based upon a) stratification as to whether or not the woman had multiple primary phyllodes tumors and b) stratification as to whether or not the phyllodes tumor was malignant, these additional efforts remain warranted. With a total of 80 cases (79 alive, 1 deceased) now available for linked analysis, plans for laboratory testing are now being developed. The demographics for these 80 cases are:

age range 16 to 69, mean 35 y/o;
60 Caucasian, 11 Latino, 5 Black, 4 Asian.

The laboratory analysis plan will be refined based on any etiologic hypotheses that may be raised as a consequence of the geographic analyses now underway.

CONCLUSIONS

We have developed important descriptive epidemiologic data concerning the phyllodes tumor cases, in terms of patient profile, place and time of occurrence, and natural history. Given the relatively young ages at which these phyllodes tumors have occurred, it is noteworthy that there was no suggestion of a sexually transmissible infectious cause for the tumors. Adequate surgical resection margins were associated with a low tumor recurrence rate.

Our evolving data suggest relatively localized clustering with some individual women at particular biologic risk. One in seven cases (14%, 16/114) had multiple phyllodes tumors diagnosed either simultaneously or over our limited period of follow-up. In contrast, multiple primary phyllodes tumors have been reported rarely. We identified only 18 such cases in the literature, excluding our series. These multiple primaries tended to be present at the time of initial phyllodes diagnosis, with the tumors bilateral. Among those who later developed their second primary, the interval has been relatively short.

Although the elevated relative incidence in Bergen County may in part reflect under-ascertainment as well as under-diagnosis of cases in the surrounding hospitals, it seems likely that both environmental and genetic factors may potentially be placing women at risk for phyllodes tumors.

REFERENCES

1. Keelan PA, Myers JL, Wold LE, Katzmann JA, Gibney DJ. Phyllodes tumor: clinicopathologic review of 60 patients and flow cytometric analysis in 30 patients. *Hum Pathol* 1992; 23:1048-1054.
2. Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. *Cancer* 1993; 71:3020-3024.
3. Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* 1996; 77:910-916.
4. Shimizu K, Masawa N, Yamada T, Okamoto K, Kanda K. Cytologic evaluation of phyllodes tumors as compared to fibroadenomas of the breast. *Acta Cytol* 1994; 38:891-897.
5. Weiss SH, Stahl RE, Skurnick JH, Zhao C, Sanchez MA. The epidemiology of phyllodes tumors of the breast in northern New Jersey. The Department of Defense Breast Cancer Program Meeting Era of Hope 1997; 1:25-26.
6. Rosai J. Breast pathology. In: Ackerman's *Surgical Pathology*. Ed. 8. St. Louis: Mosby, 1996:1628-1630.
7. Treves N, Sunderland DA. Cystosarcoma phyllodes of the breast: a malignant and a benign tumor. A clinicopathological study of seventy-seven cases. *Cancer* 1951; 4:1286-1332.
8. Jacquez GM, Waller LA, Grimson R, Wartenberg D. The analysis of disease clusters, part I: state of the art. *Infect Control Hosp Epidemiol* 1996; 17:319-327.
9. Jacquez GM, Grimson R, Waller LA, Wartenberg D. The analysis of disease clusters, part II: introduction to techniques. *Infect Control Hosp Epidemiol* 1996; 17(6):385-397.
10. Birch JM. Li-Fraumeni Syndrome. *Eur J Cancer* 1994; 30A(13):1935-1941.

FINAL REPORT 9 / 98, GRANT No. DAMD17 - 94 - J - 4423

11. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. *Cancer Res* 1994; 54:1298-1304.
12. Sidransky D, Tokino T, Helzlsouer K, et al. Inherited p53 gene mutations in breast cancer. *Cancer Res* 1992; 52:2984-2986.
13. Mazoyer S, Lalle P, Moyret-Lalle C, et al. Two germ-line mutations affecting the same nucleotide at codon 257 of p53 gene, a rare site for mutations. *Oncogene* 1994; 9:1237-1239.
14. Kim CJ, Kim WH. Patterns of p53 expression in phyllodes tumors of the breast--an immunohistochemical study. *Journal of Korean Medical Science* 1993; 8:325-328.
15. Shabalova IP, Chemeris GJ, Ermilova VD, Rodionova LM, Pavlikova NA. Phyllodes tumour: cytologic and histologic presentation of 22 cases, and immunohistochemical demonstration of p53. *Cytopathology* 1997; 8:177-187.

BIBLIOGRAPHY OF PUBLICATIONS

Centurion SA, Weiss SH. Epidemiological evaluation of the geographic bounds of a cluster of cystosarcoma phyllodes tumors. 1995 Summer Research Abstract Book, New Jersey Medical School, Newark, NJ 1995.

Hou JR, Weiss SH. Cystosarcoma phyllodes: an epidemiological assessment of the recurrence rate of a rare breast tumor. 1995 Summer Research Abstract Book, New Jersey Medical School, Newark, NJ 1995.

Weiss SH, Stahl RE, Hou J, et al. Cystosarcoma phyllodes breast tumors among women in northern New Jersey: an unusual cluster (abstract). The Oncology Society of New Jersey & the Academy of Medicine of New Jersey 1996; March 6, 1996.

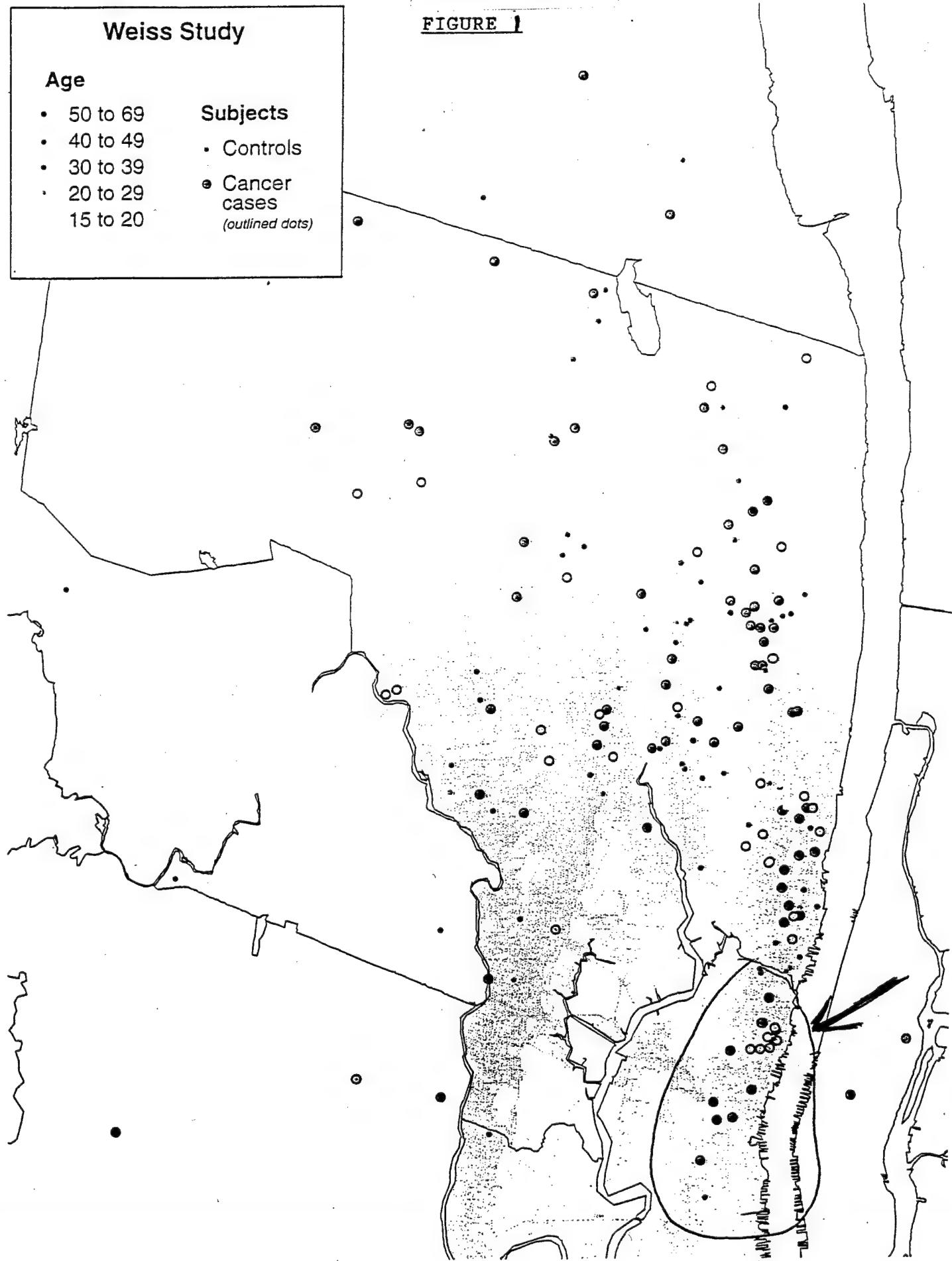
Weiss SH, Stahl RE, Skurnick JH, Zhao C, Sanchez MA. The epidemiology of phyllodes tumors of the breast in northern New Jersey. The Department of Defense Breast Cancer Program Meeting Era of Hope 1997; 1:25-26.

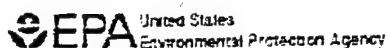
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LIST OF PERSONNEL

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FIGURE 1



Surf Your Watershed

COUNTY INFORMATION

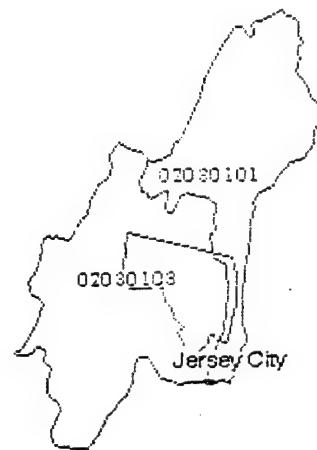
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Bergen, NJ

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This county crosses 2 watersheds.

Environmental Profile

(provided by EPA's Center for Environmental Information and Statistics (CEIS))

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Find environmental information for each of these watersheds:

- o 02030101 Lower Hudson; states: CT NJ NY
- o 02030103 Hackensack-Passaic; states: NJ NY

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Hudson, NJ

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This county crosses 3 watersheds.

Environmental Profile

(provided by EPA's Center for Environmental Information and Statistics (CEIS))

Where does my drinking water come from?

Find environmental information for each of these watersheds:

- o 02030101 Lower Hudson; states: CT NJ NY
- o 02030103 Hackensack-Passaic; states: NJ NY
- o 02030104 Sandy Hook-Staten Island; states: NJ NY

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Metropolitan Areas:

Environmental Profile

Find general information integrated for this specific watershed

Assessments of Watershed Health

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- [Superfund Sites](#) (Source: [CERCLA](#) - Comprehensive Environmental Response, Compensation, and Liability Act)

[EnviroMapper for Watersheds](#) - (interactive mapping tool)

Water

Figure 3

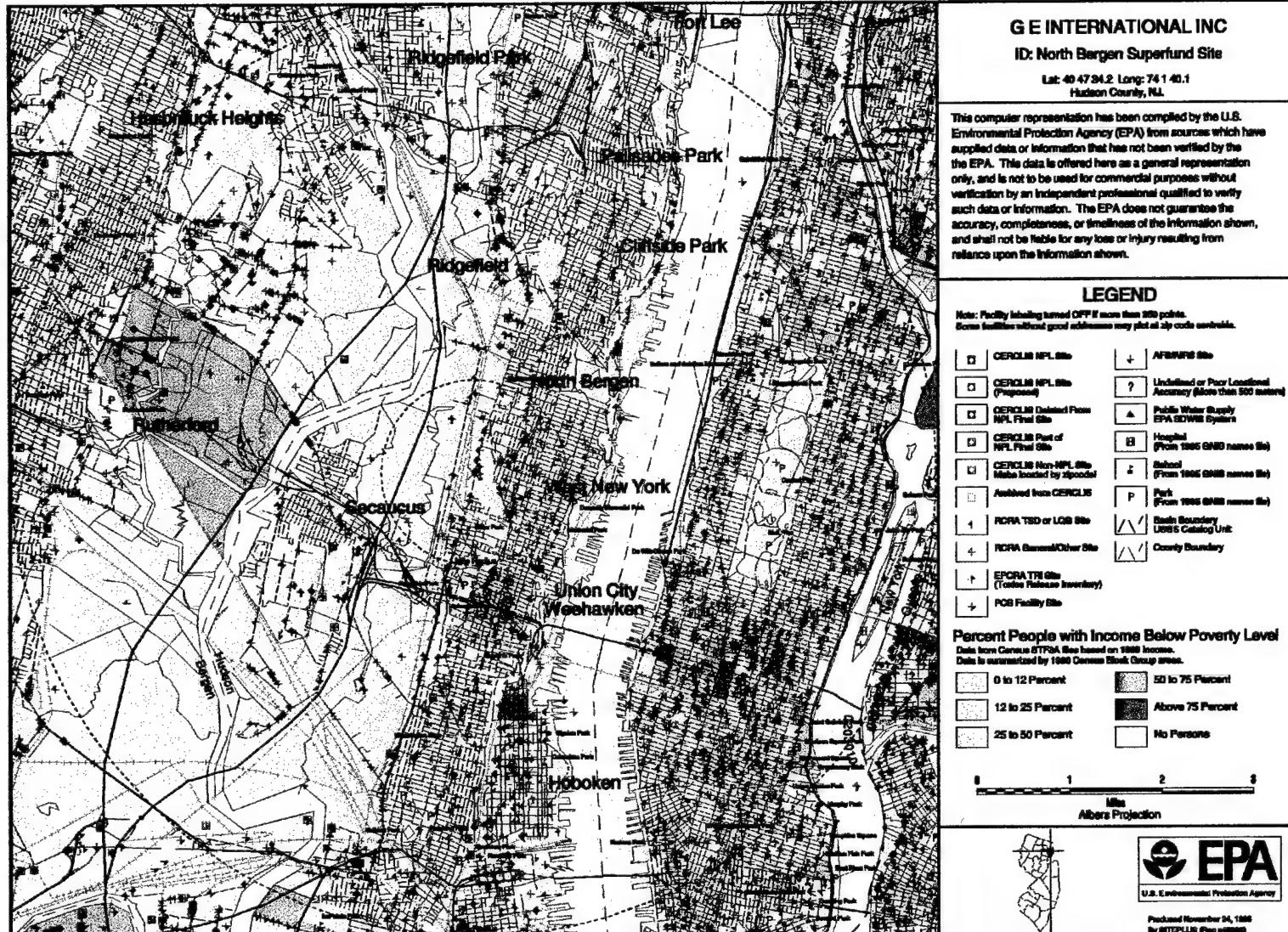
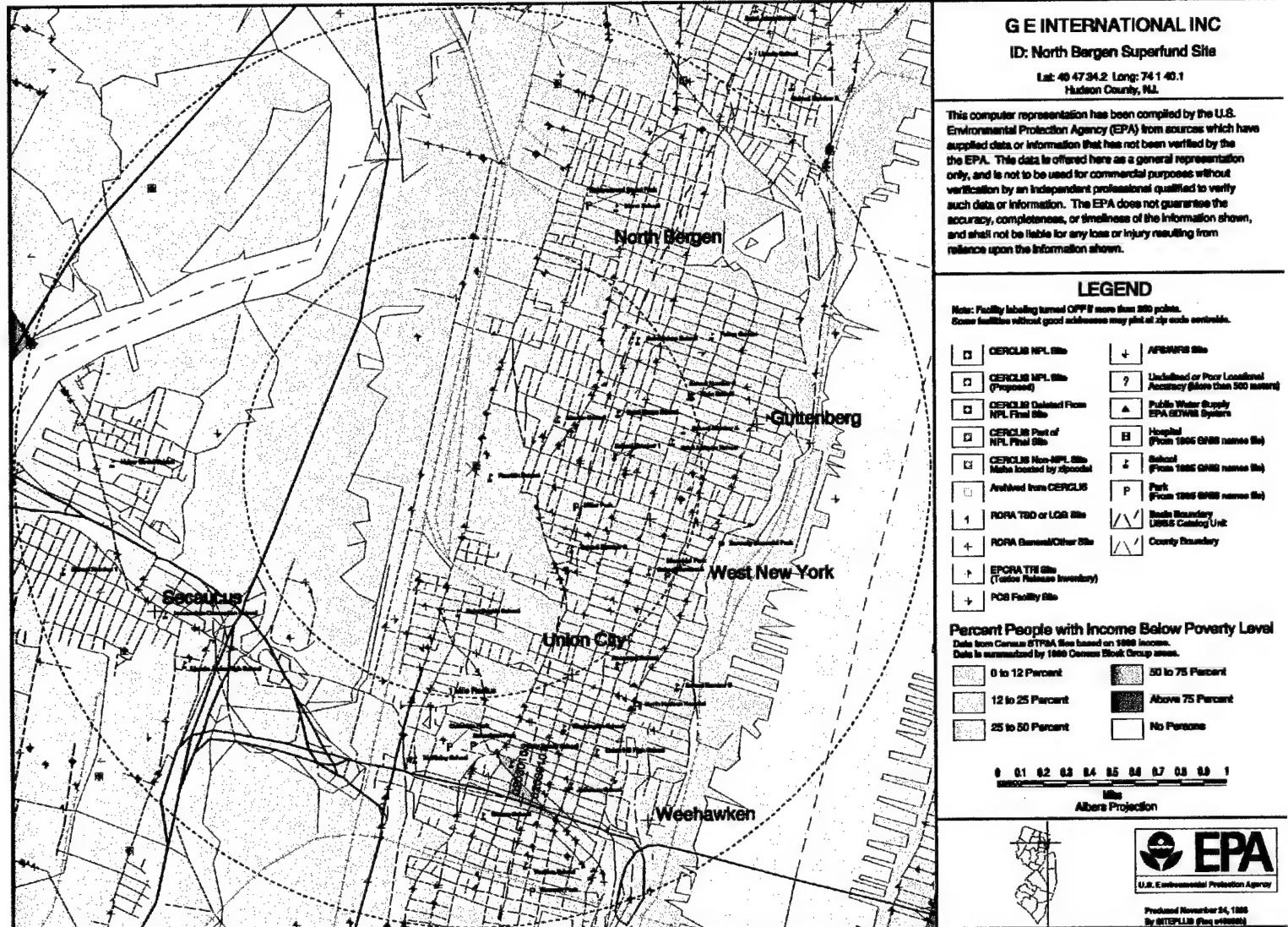


Figure 4



Weiss Study

Types of Tumor

One Tumor:

○ Benign

● Malignant

Multiple: = red rimmed

○ Benign

● Malignant (one)

FIGURE 5

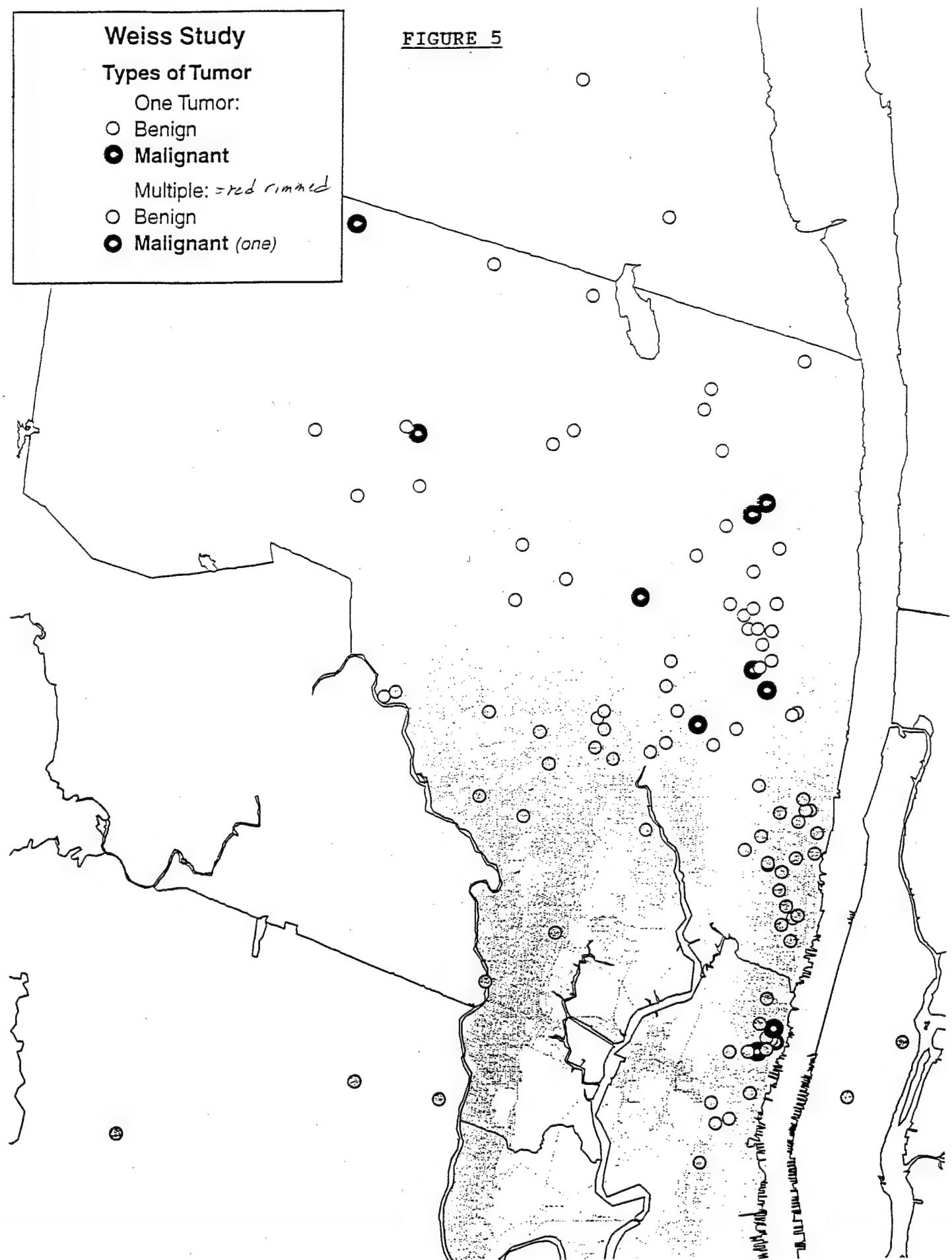


TABLE 1: Literature Review of Phyllodes Breast Tumor Case Series

Author	Year Pub- lished	Country, State	Source: H=Hospital C=Country	Age Range	No. of Patients	Not Known	Benign	Border- line	Malignant	Bilateral	Multiple Phyllodes Tumors		Local/Distant Recurrences	
											Documented Multiple	Possible Multiple		
Lester ¹	1954	1912- 1952	USA, NY	H/SKMCC	13- 88	58	-	29	8	25	2	0	1	11
Treves & Sutherland ²	1951	1930- 1949	USA, NY	H/SKMCC	15-72	77	-	41	18	18	0	0	0	22
McDivitt ³ and Treves ⁴	1967 & 1964	1949- 1965	USA, NY	H/SKMCC	16-68	73	-	59	0	14	0	0	0	12
Rajan ⁵	1998	1982- 1996	USA, NY	H/SKMCC	10-24	45	-	34	0	11	0	0	0	7
Liberman ⁶	1996	1986- 1995	USA, NY	H/SKMCC	24-83	46	-	32	0	19	1*	0	0*	3
Pietruszka ⁷ & Maior ⁸	1978 & 1968- 1977	1945- 1977	USA, PA	H/ Pittsburgh	14-67	42	-	18	5	19	0	0	1	10
Bernstein ⁹	1993	1972- 1989	USA, CA	Los Angeles County	18- 89	154	-	0	0	154	0	0	0	Ns
Norris ¹⁰	1967	Ns - 1988 & 1987	USA, DC	H/District of Columbia	15-86	94	94	Ns	Ns	1	0	0	Ns	28
Murad ¹¹ and Hines ¹²	1959- 1978	1959- 1981	USA, IL	H/Chicago	16- 82	25	-	15	0	10	0	0	0	10
Hart ¹³	1976	Ns -	USA, MI	H/Ann Arbor	19-64	26	-	12	0	14	0	0	0	8
Keelan ¹⁴	1992	1913- 1990	USA, MN	H/Rochester	16-72	60	60	Ns	Ns	1	0	0	0	11
Halverson ¹⁵	1974	1940- Ns -	USA, MO	H/St. Louis	17-82	16	-	2	6	8	0	0	0	7
Ward ¹⁶	1986	1980	USA, TX	H/Houston	15-77	26	26	Ns	Ns	0	0	0	0	9

Author	Year Published	Year Range	Country, State	Source: H=Hospital C=Country	Age Range	No. of Patients	Not Known	Benign	Border-line	Malignant	Pathology				Local/ Distant Recurrences
											Bilateral	Documented Unilateral	Possible Unilateral	Multiple	
Rix ¹⁷	1971	1954 -1966	Canada	H/ Vancouver	35-77	20	-	0	0	20	0	0	0	0	6
McGregor ¹⁸	1994	1972 -1992	Canada	H/ Vancouver	14-86	38	38	Ns	Ns	0	0	0	0	0	11
Hoptins ¹⁹	1994	1960 -1990	Canada	H/Toronto	22 -71	14	-	14	0	0	0	0	0	0	5
Prati ²⁰	1993	1970 -1989	Italy	H/Verona	17-60	17	-	17	0	0	1	0	0	0	3
Ciatto ²¹	1992	1977 -	Italy	H/Florence & Genova	<40 - >69	59	-	22	12	25	0	0	0	0	19
Grigioni ²²	1982	Ns - 1981	Italy	H/Bologna	13-57	20	-	10	0	10	0	0	0	1	7
Zurrida ²³	1992	1970 - 1989	Italy	H/Milan	9 ->50	216	-	140	46	30	0	0	0	0	27
Bennett ²⁴	1992	1970 -	UK	C/London	20-75	30	-	14	5	11	0	0	0	0	5
Moffat ²⁵	1995	1975 -	UK	H/ Nottingham	23-92	32	-	23	4	5	1	0	0	0	6
Stebbing ²⁶	1995	1981 -	UK	H	15-67	32	-	24	6	3	0	0	0	1	8
Christensen ²⁷ & Christensen ²⁸ Terrier ²⁹	1993 & 1986 - 1989	1977 - 1989	Denmark	C	13-94	73	-	36	19	18	0	0	0	0	15
VanZyl ³⁰	1989	1972 - 1988	France	H	17-87	17	-	0	0	17	0	0	0	0	7
Reinliss ³¹	1996	1952 - 1988	Poland	H	19-76	170	-	92	19	59	0	0	0	0	37
Popescu ³²	1991	1960 - 1989	Romania	H	16-80	19	-	15	0	4	0	1	0	0	2
Aranda ³³	1994	1987 - 1993	Spain	H	32 -73	28	-	14	6	8	0	0	0	0	7

Author	Year Pub-listed	Year Range	Country, State	Source: H=Hospital C=Country	Age Range	No. of Patients	Not Known	Benign	Border-line	Malignant	Pathology			At Initial Presentation: Number of Patients with Multiple Phyllodes Tumors	Local/ Distant Recurrences
											Bilateral	Documented	Possible Unilateral	Multiple	
Cohn-Cedermark ³⁴	1991	1958 -1986	Sweden	C	18-85	77	15	13	0	49	0	0	0	0	≤31
Kanis ³⁵	1990	1969 -1988	Japan	H	15-62	34	-	22	8	4	1	1	0	0	7
Chua ³⁶	1988	1978 -1984	Singapore	C	13-63	106	-	98	6	3	1	0	0	0	20
Totals:	32	1912 - 1996	13 Countries	9-92	1765	233	804	172	567	9	2	4	4	372	
Totals: excluding the Los Angeles County series³ but including the later primary tumors (*)	31			1611	233	804	172	413	11	2	5	5	372		(21.1%)
						(13.8%)	(45.6%)	(9.7%)	(32.1%)	(0.51%)	(0.11%)	(0.23%)			

* Over the course of follow-up, one additional patient noted. Although the 1964 study by Treves⁴ mentions one case in which a contralateral phyllodes tumor was found during follow-up, a subsequent report by McDivitt³ does not (which may reflect a differing interpretation of the pathology of that new tumor); it is nevertheless counted in the second summary total

Ns: not stated

SKMCC = Sloan Kettering Memorial Cancer Center

Number of Studies by Region: USA 13, Canada 3, Europe 14, and Far East 2

REFERENCES FOR TABLE 1: Literature Review of Phyllodes Breast Tumor Case Series

1. Lester J, Stout AP. Cystosarcoma phyllodes. *Cancer* 1954; 7:335-353.
2. Treves N, Sunderland DA. Cystosarcoma phyllodes of the breast: a malignant and a benign tumor. A clinicopathological study of seventy-seven cases. *Cancer* 1951; 4:1286-1332.
3. McDivitt RW, Urban JA, Farrow JH. Cystosarcoma phyllodes. *Johns Hopkins Med J* 1967; 120:33-45.
4. Treves N. A study of cystosarcoma. *Ann NY Acad Sci* 1964; 114:922-936.
5. Rajan PB, Cranor ML, Rosen PP. Cystosarcoma phyllodes in adolescent girls and young women: a study of 45 patients. *Am J Surg Pathol* 1998; 22:64-69.
6. Liberman L, Bonnaccio E, Hamele-Bena D, Abramson AF, Cohen MA, Dershaw DD. Benign and malignant phyllodes tumors: mammographic and sonographic findings. *Radiology* 1996; 198:121-124.
7. Pietruszka M, Barnes L. Cystosarcoma phyllodes: a clinicopathologic analysis of 42 cases. *Cancer* 1978; 41:1974-1983.
8. Maier WP, Rosemond GP, Wittenberg P, Tassoni EM. Cystosarcoma phyllodes mamma. *Oncology* 1968; 22:145-157.
9. Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. *Cancer* 1993; 71:3020-3024.
10. Norris HJ, Taylor HB. Relationship of histologic features to behavior of cystosarcoma phyllodes: analysis of 94 cases. *Cancer* 1967; 20:2090-2099.
11. Murad TM, Hines JR, Beal J, Bauer K. Histopathological and clinical correlations of cystosarcoma phyllodes. *Arch Pathol Lab Med* 1988; 112:752-756.
12. Hines JR, Murad TM, Beal IM. Prognostic indicators of cystosarcoma phyllodes. *Am J Surg* 1987; 153:276-280.
13. Hart WR, Bauer RC, Oberman HA. Cystosarcoma phyllodes. A clinicopathologic study of twenty six hypercellular periductal stromal tumors of the breast. *Am J Clin Pathol* 1978; 70:211-216.
14. Keelan PA, Myers JL, Vold LE, Katzmann JA, Gibney DJ. Phyllodes tumor: clinicopathologic review of 60 patients and flow cytometric analysis in 30 patients. *Hum Pathol* 1992; 23:1048-1054.
15. Halverson JD, Hori-Rubaina JM. Cystosarcoma phyllodes of the breast. *Am Surg* 1974; 40:295-301.
16. Ward RM, Evans HL. Cystosarcoma phyllodes; a clinicopathologic study of 26 cases. *Cancer* 1986; 58:2282-2289.
17. Rix DB, Tredwell SJ, Forward AD. Cystosarcoma phyllodes (cellular intracanalicular fibroadenoma): clinical-pathological relationships. *Canadian J Surg* 1971; 14:31-37.

18. McGregor GI, Knowling MA, Este FA. Sarcoma and Cystosarcoma phyllodes tumors of the breast--a retrospective review of 58 cases. *Am J Surg* 1994; 167:477-480.
19. Hopkins ML, McGowan TS, Rawlings G, et al. Phyllodes tumor of the breast: a report of 14 cases. *J Surg Oncol* 1994; 56:108-112.
20. Modena S, Prati G, Mainente M, et al. Phyllodes tumor of the breast: problems of differential diagnosis and therapeutic approach from an analysis of 17 cases. *Eur J Surg Oncol* 1993; 19:70-73.
21. Ciatto S, Bonardi R, Cataliotti L, Cardona G. Phyllodes tumor of the breast: a multicenter series of 59 cases. Coordinating Center and Writing Committee of FONCAM (National Task Force for Breast Cancer), Italy. *Eur J Surg Oncol* 1992; 18:545-549.
22. Grigioni WF, Santini D, Grassigli A, et al. A clinicopathologic study of cystosarcoma phyllodes. Twenty cases report. *Arch Anat Cytol Path* 1982; 30(5-6):303-306.
23. Zurrida S, Bartoli C, Galimberti V, et al. Which therapy for unexpected phyllodes tumour of the breast? *Eur J Cancer* 1992; 28:654-657.
24. Bennett IC, Khan A, De Freitas R, Chaudary MA, Millis RR. Phyllodes tumours: a clinicopathological review of 30 cases. *Australian & New Zealand Journal of Surgery* 1992; 62:628-633.
25. Moffat CJ, Pinder SE, Dixon AR, Elston CW, Blamey RW, Ellis IO. Phyllodes tumours of the breast: a clinicopathological review of thirty-two cases. *Histopathology* 1995; 27:205-218.
26. Stebbing JF, Nash AG. Diagnosis and management of phyllodes tumour of the breast: experience of 33 cases at a specialist centre. *Annals of the Royal College of Surgeons of England* 1995; 77:181-184.
27. Christensen L, Schiødt T, Blichert-Toft M. Sarcomatoid tumours of the breast in Denmark from 1977 to 1987. A clinicopathological and immunohistochemical study of 100 cases. *Eur J Cancer* 1993; 29A:1824-1831.
28. Christensen L, Nielsen M, Madsen PM. Cystosarcoma phyllodes: a review of 19 cases with emphasis on the occurrence of associated breast carcinoma. *Acta Path Microbiol Immunol Scand* 1986; Sec A;94:35-41.
29. Terrier P, Terrier-Lacombe MJ, Mouriesse H, Friedman S, Spielmann M, Contesso G. Primary breast sarcoma: a review of 33 cases with immunohistochemistry and prognostic factors. *Breast Cancer Res Treat* 1989; 13:39-48.
30. van Zyl JA, Muller AG, von der Heyden U. Phyllode tumours of the breast. A review of 21 cases. *S Afr J Surg* 1989; 27:168-170.
31. Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* 1996; 77:910-916.

32. Popescu I, Serbanescu M, Ivășescu C. Phylloides tumours of the breast. A clinicopathologic study of 19 cases. *Zentralbl Chir* 1991; 116:327-336.
33. Aranda FI, Laforga JB, Lopez JI. Phylloides tumor of the breast. An immunohistochemical study of 28 cases with special attention to the role of myofibroblasts. *Pathology, Research & Practice* 1994; 190:474-481.
34. Cohn-Cedermark G, Rutqvist LE, Rosendahl I, Silfversward C. Prognostic factors in cystosarcoma phyllodes. A clinicopathologic study of 77 patients. *Cancer* 1991; 68:2017-2022.
35. Kario K, Maeda S, Mizuno Y, Makino Y, Tankawa H, Kitazawa S. Phyllodes tumor of the breast: a clinicopathologic study of 34 cases. *J Surg Oncol* 1990; 45:46-51.
36. Chua CL, Thomas A. Cystosarcoma phyllodes tumors. *Surgery, Gynecology & Obstetrics* 1988; 166:302-306.